1.1 Scientific Abstract

An American male dies of prostate cancer every 14 minutes, 39,200 men/year (1). While surgery or radiation can cure early-stage organ-confined prostate cancer, no curative therapy exists for locally advanced or metastatic disease (2). The ten year overall survival rate for patients with locally recurrent disease is 35%, and the disease invariably progresses to the development of hormone refractory metastases (3). The standard of care for patients who experience a recurrence following definitive radiotherapy to the prostate, the target population of this study, includes supportive care with hormonal ablation, or treatment with investigational therapies (4).

The scientific rationale for this clinical trial of CN706 translates from 4 years of research at Calydon, Inc. and from NIH-sponsored research at the Johns Hopkins Oncology Center (5) . Prostate-specific antigen (PSA) is found in over 95% of prostate carcinomas and forms the basis of the most widely used diagnostic marker of disease progression in all of cancer (6). Minimal constructs containing portions of the enhancer/promotor elements that regulate PSA gene expression have been inserted into the adenovirus 5 (Ad5) genome so as to drive the expression of the E1A gene (5,7). The E1A gene product is required for virus replication. The resultant virus, CN706, is restricted in its replication to PSA-expressing cells. Thus, CN706 is an oncolytic cytoreductive therapy.

Peer-reviewed, preclinical studies have confirmed that CN706 results in selective cytotoxicity towards PSA-expressing cells both *in vitro* and *in vivo*. Intratumoral injections of CN706 at doses in excess of 1 x 10^8/mm^3 resulted in the regression of large (1 cm diameter) LNCaP prostate cancer xenograft tumors within 5 weeks and led to elimination of serum PSA levels (5). No treatment-related deaths were seen in preclinical toxicology studies of the intraperitoneal and intraprostatic administration of CN706. As would be expected for Ad5, no evidence of germ-line transmission of CN706 was detected. No abnormalities in testicular histopathology were noted following the intraprostatic injection of CN706.

The IND for this proposed single-center, non-randomized, open-label, Phase I dose-escalation study of the intraprostatic injection of CN706 has been reviewed by FDA and is active. With the concurrence of the FDA, the primary objective of the study will be to determine the maximum tolerated dose of CN706 using NCI common toxicity criteria. Secondary objectives include evaluation of antitumor activity, time to disease progression, monitoring of the immune response to CN706, and evaluation of the pharmacokinetics and biodistribution of the virus.

CN706 will be administered using standard of care methodology for the placement of ^{125}I seeds for interstitial radiotherapy of the prostate (brachytherapy). The methodology includes anatomical definition of the prostate, volumetric treatment planning, and injection using ultrasound guidance. Patients under spinal anesthesia will receive 10 intraprostatic injections of CN706 on Day 1 of the study (20-40 injections are commonly employed for the placement of ^{125}I seeds). The dose levels being tested in this study are consistent with dose levels at which efficacy was seen in preclinical studies and are supported by the results of preclinical toxicology studies. The starting dose level for the trial (1 X 10^{11} particles/prostate) is 100-fold lower than the no-effect dose of CN706 administered intraperitoneally to Cotton rats and 50-fold lower than the lowest dose of CN706 administered directly into the prostate of Copenhagen rats. Three patients will be treated at each of five dose levels in increasing half log dose increments. Intraprostic treatment with CN706 offers the potential of specifically targeting the cytotoxicity of adenovirus to prostate carcinoma cells and obtaining cytotoxicity through tissue-specific virus replication.